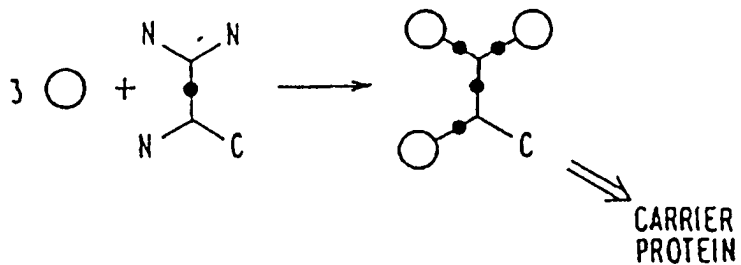
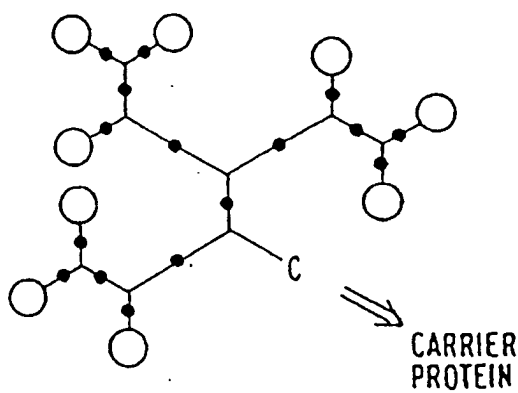
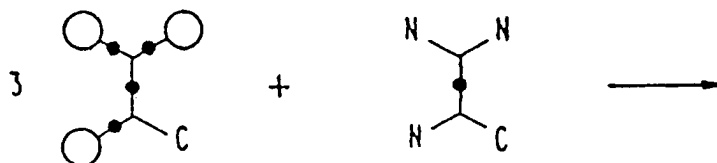



SCHEME 1

TRIVALENT
CONJUGATE



NONVALENT
CONJUGATE



 T_n -ANTIGEN

• AMIDE BOND

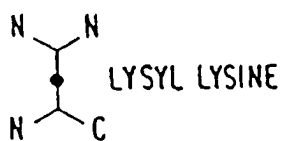


FIG. 1 A

SCHEME II

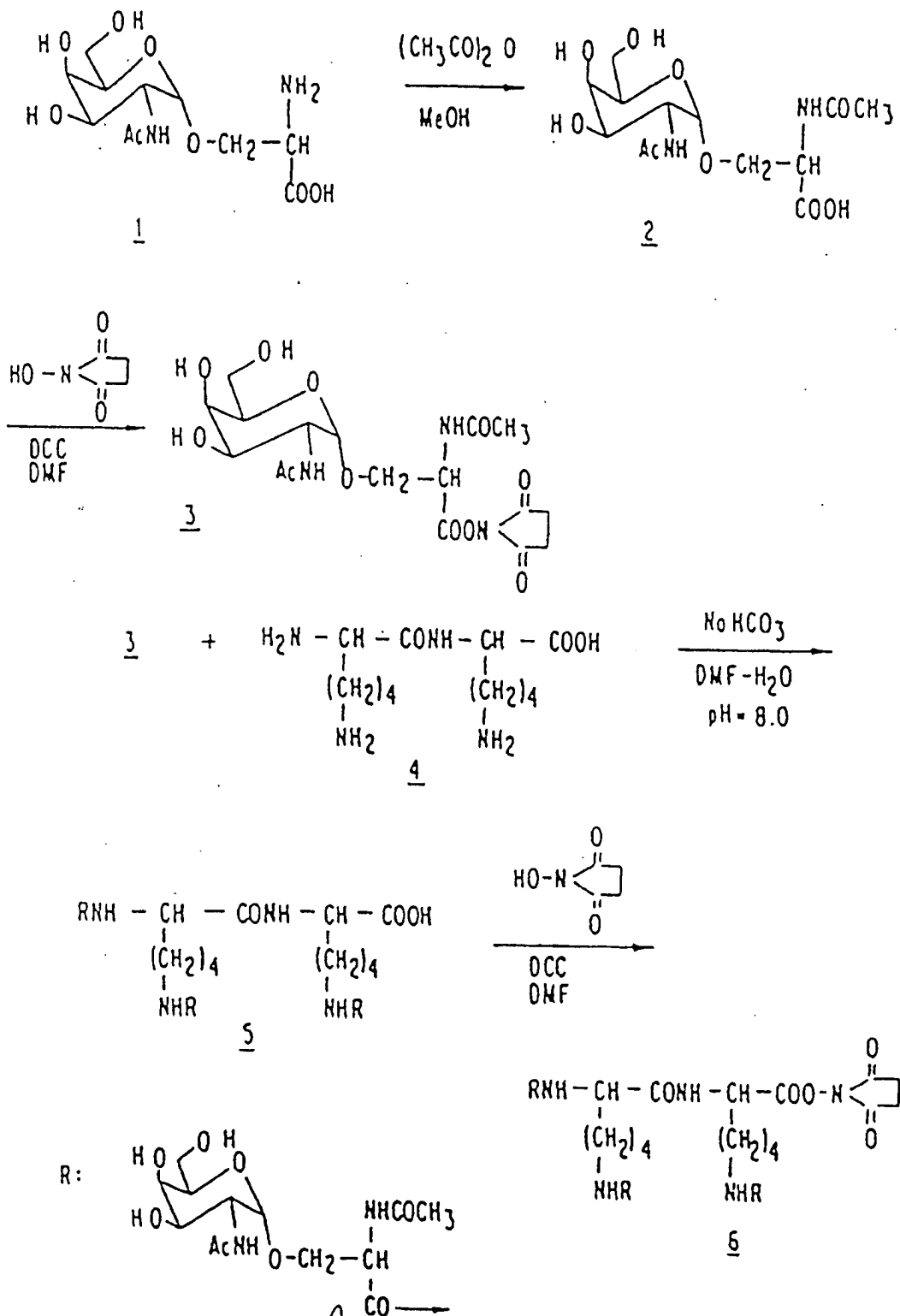


FIG.

1B

SYNTHESIS OF ANTIGEN CLUSTERS.

General formula: $\text{Ac}-(\text{Ser})_m-(\text{Thr})_n-\text{NH}-(\text{CH}_2)_3-\text{COOH}$
 $(m + n \leq 3)$

Examples: $\text{Ac-Ser-NH}-(\text{CH}_2)_3-\text{COOH}$ 5
 *

$\text{Ac-Thr-NH}-(\text{CH}_2)_3-\text{COOH}$
 *

$\text{Ac-Ser-Ser-NH}-(\text{CH}_2)_3-\text{COOH}$
 * *

$\text{Ac-Ser-Ser-Ser-NH}-(\text{CH}_2)_3-\text{COOH}$
 * * *

$\text{Ac-Ser-Thr-Thr-NH}-(\text{CH}_2)_3-\text{COOH}$ 6
 * * *

* : $\text{GalNAc}\alpha 1 \longrightarrow / \text{NeuAc}\alpha 2 \longrightarrow 6\text{GalNAc}\alpha 1 \longrightarrow$

FIG.

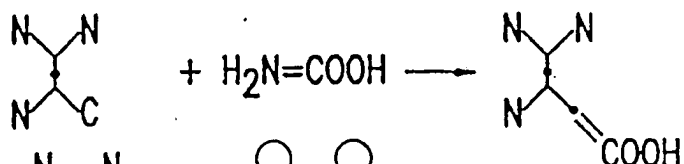
2A

CONSTRUCTION OF MULTIVALENT SYSTEMS.

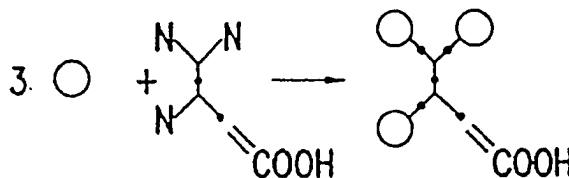
MONOVALENT
CONJUGATE



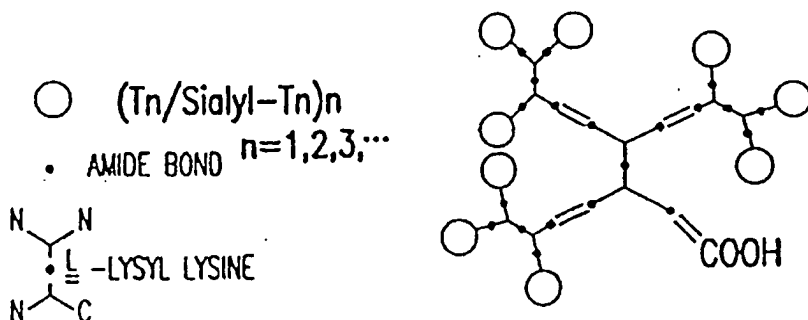
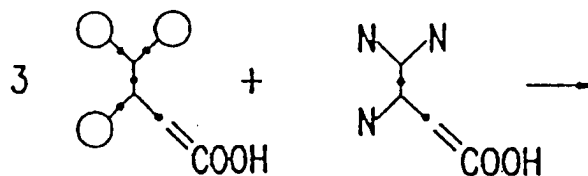
CORE STRUCTURE



TRIVALENT
CONJUGATE



NONOVALENT
CONJUGATE



$\text{H}_2\text{N}=\text{COOH}$ SPACER ARM (e.g. 4-aminobutyric acid)

FIG.

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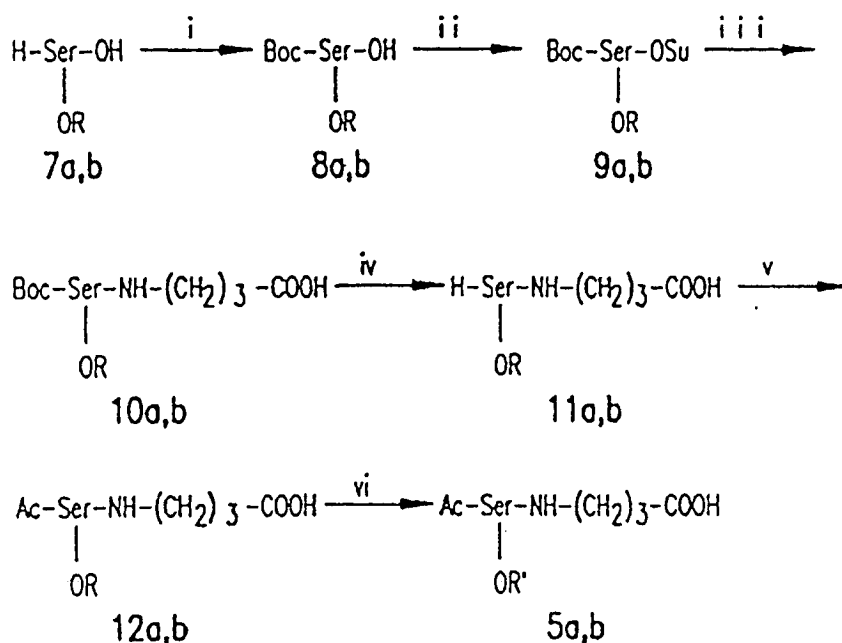
DESIGN FOR EFFECTIVE PRESENTATION OF SYNTHETIC ANTIGENS TO IMMUNE SYSTEM.

- (☐)_h — carrier protein (e.g. BSA, KLH)
- ☐ — tripalmitoyl-S-glycerylcysteinyl-seryl-serine
- ☐ — monophosphoryl lipid A
- ☐ : constructed antigen systems

FIG.

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SYNTHESIS OF 5



Reagents: i) Boc_2O , Et_3N , MeOH ; i i) NHS , EDC , CH_2Cl_2 ;
i i i) $\text{H}_2\text{N-(CH}_2\text{)}_3\text{-COOH}$, Et_3N , DMF ; iv) HCOOH ; v) Ac_2O , MeOH ;
vi) 10% 1N NaOH in MeOH , 5 min.

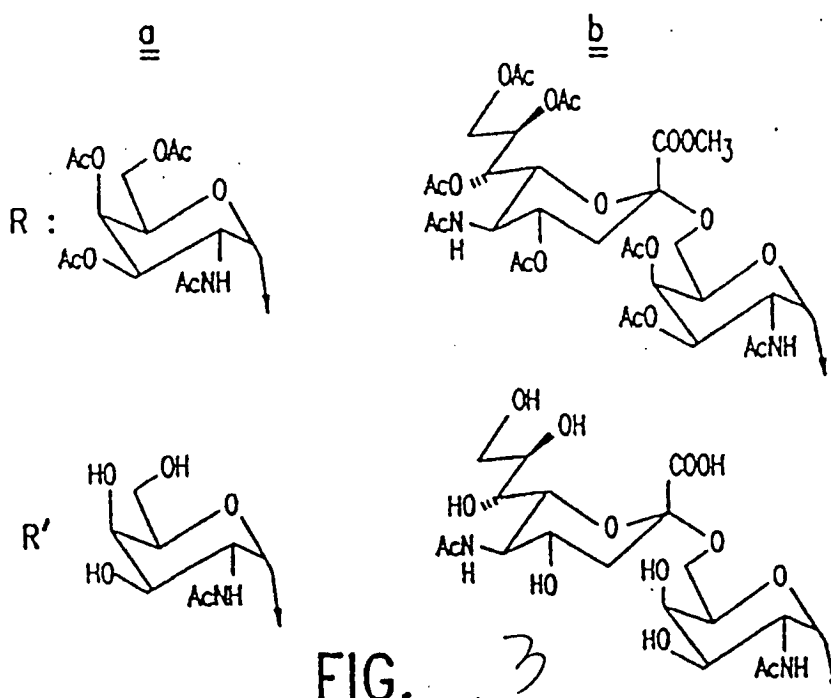
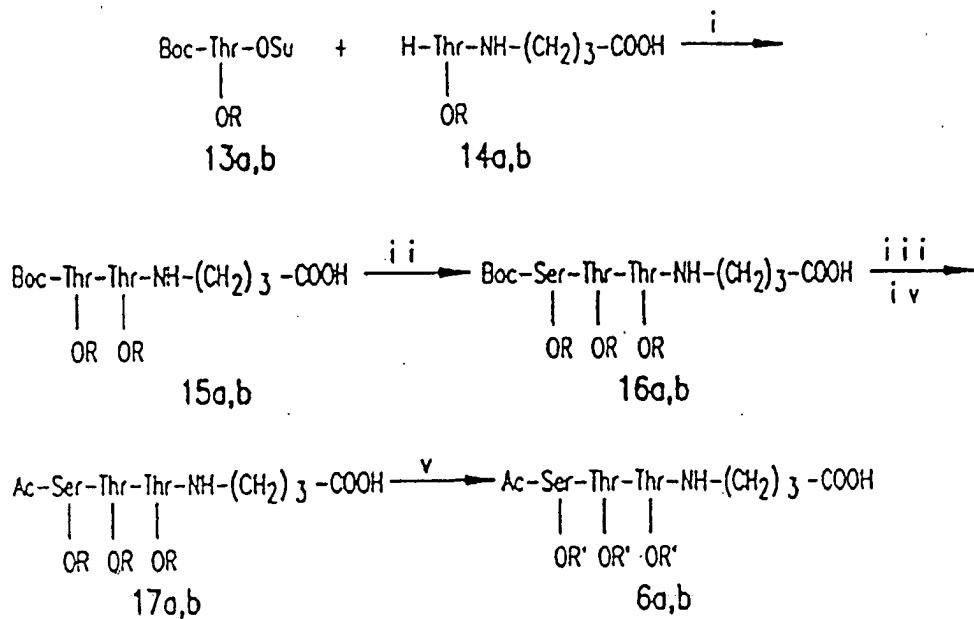


FIG. 3

SYNTHESIS OF 6



Reagents: i) Et₃N, DMF; ii) 9a,b, Et₃N, DMF; iii) HCOOH;
 iv) Ac₂O, MeOH; v) 10% 1N NaOH in MeOH, 1 h.

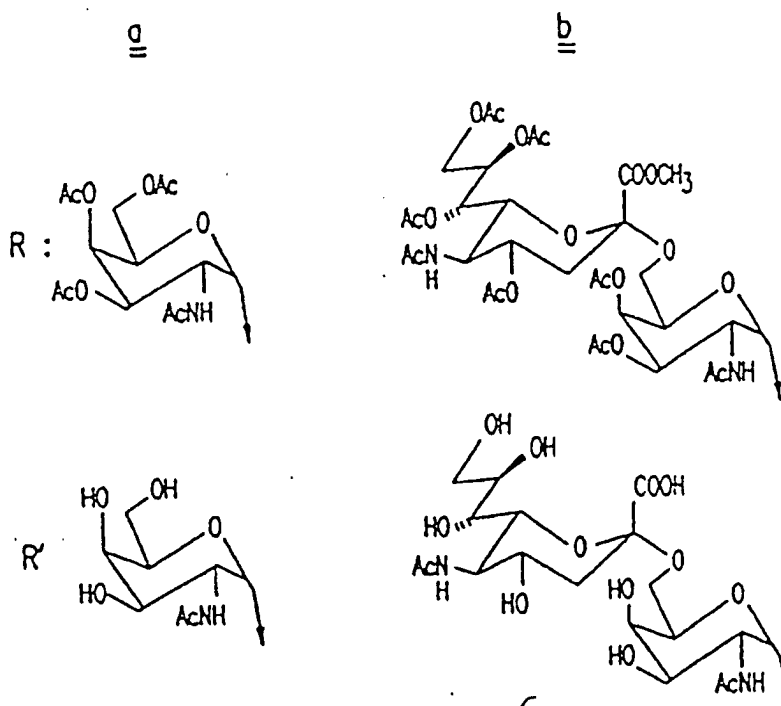
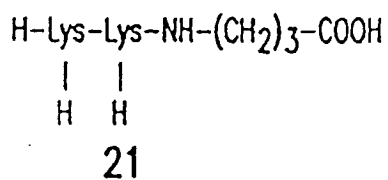
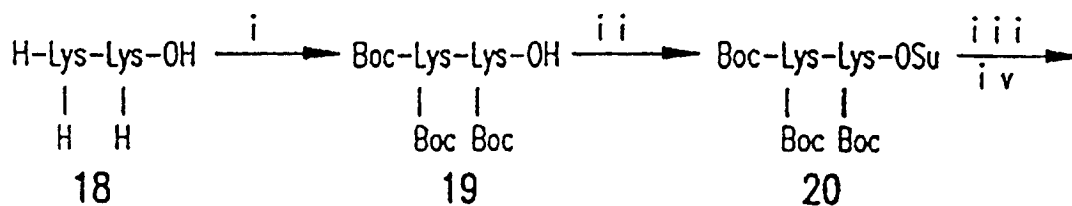


FIG. 4

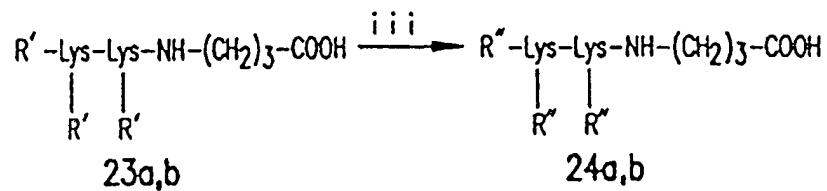
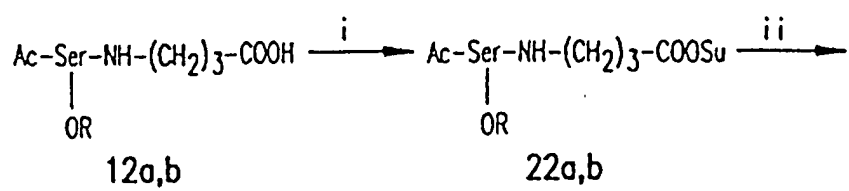
PREPARATION OF CORE STRUCTURE



Reagents: i) Boc_2O , Et_3N , MeOH ; i i) NHS , EDC , CH_2Cl_2 ;

i i i) $\text{H}_2\text{N-(CH}_2\text{)}_3\text{-COOH}$, Et_3N , DMF ; iv) HCOOH .

FIG. ~~2A~~
5A



Reagents: i) NHS, EDC, DMF; i i) 21, Et₃N, DMF-H₂O;

i i i) 10% 1N NaOH in MeOH, 5 min.

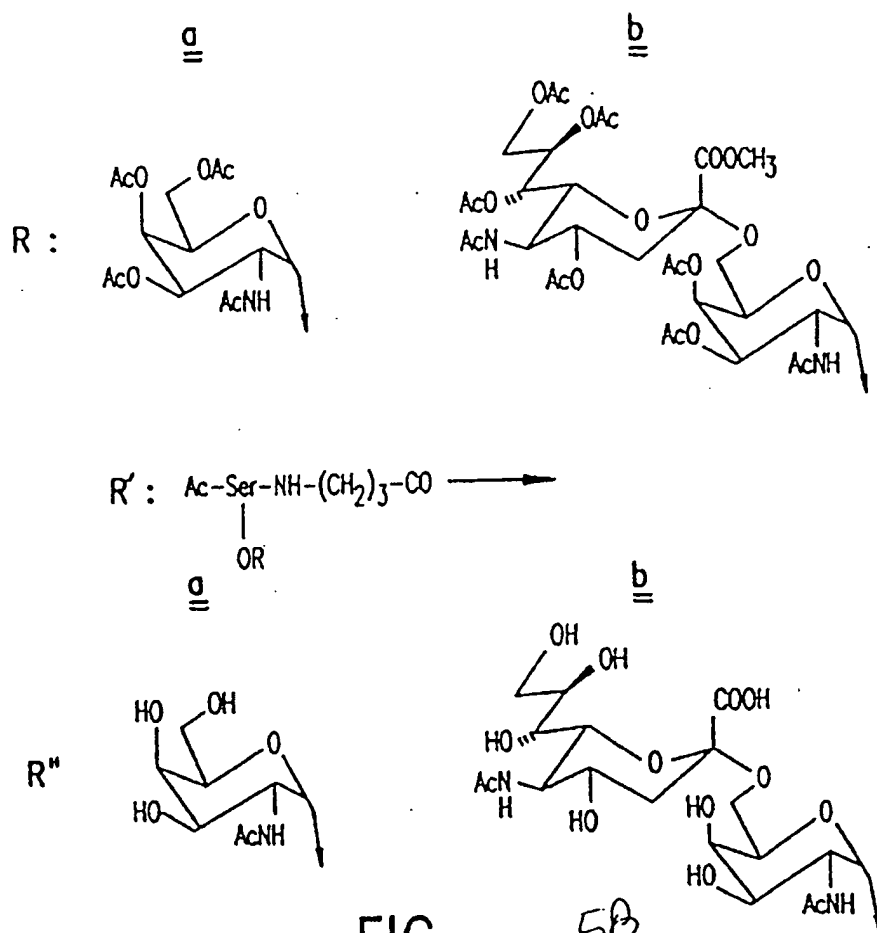
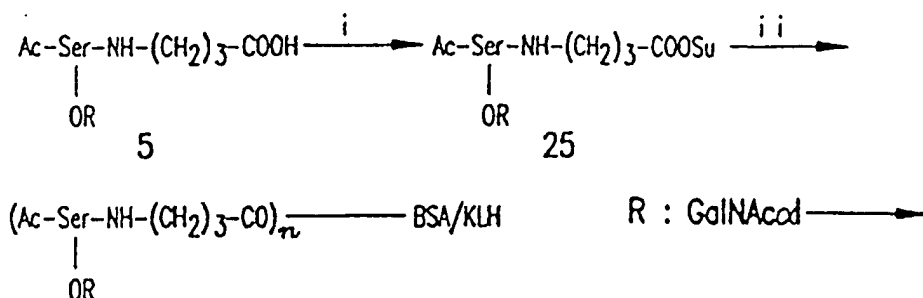


FIG.

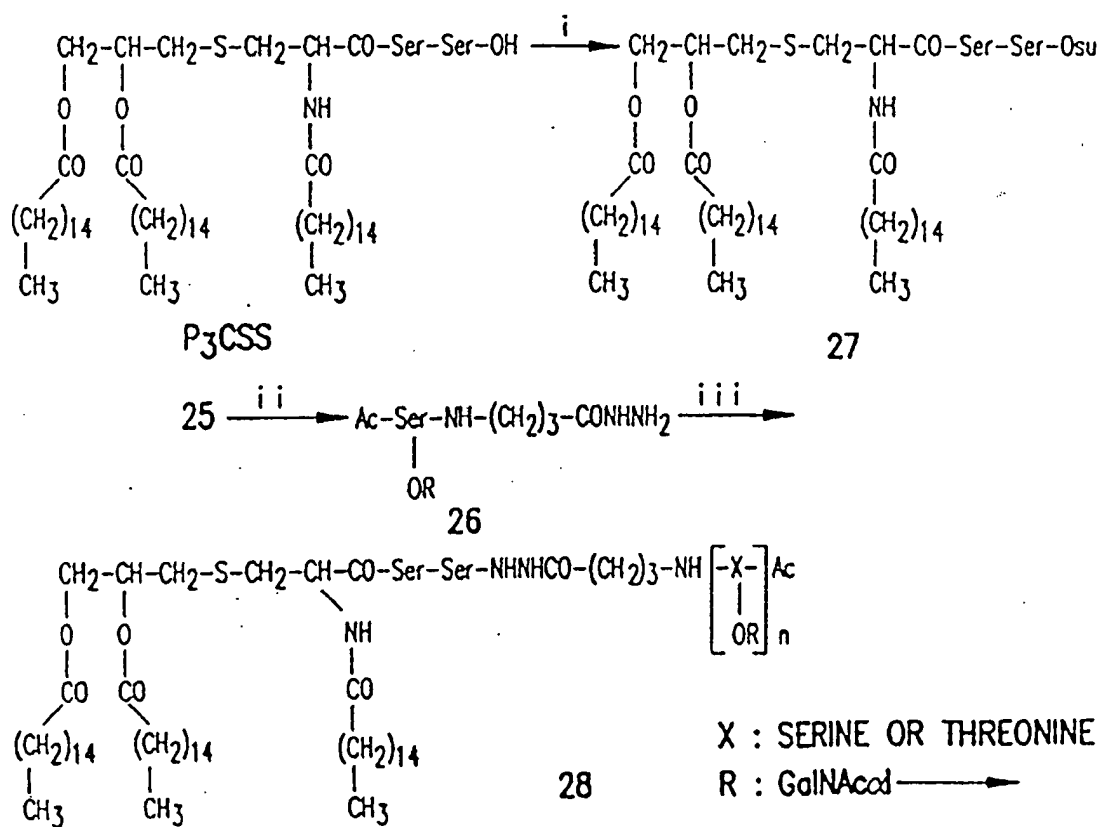
5B

CONJUGATION WITH CARRIER PROTEINS



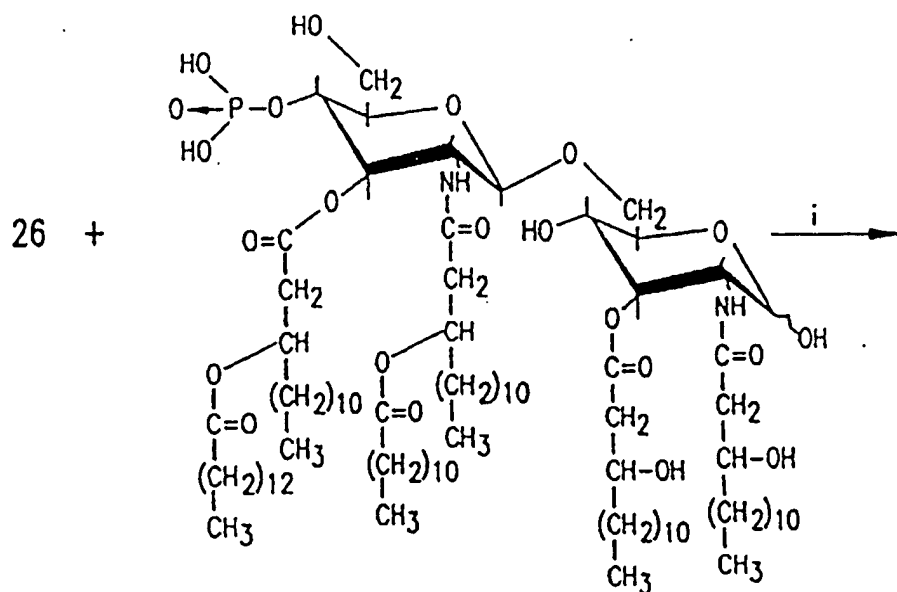
Reagents: i) NHS, EDC, DMF; ii) BSA/KLH, NaHCO₃, DMF-H₂O.

CONJUGATION WITH NON-MACROMOLECULES

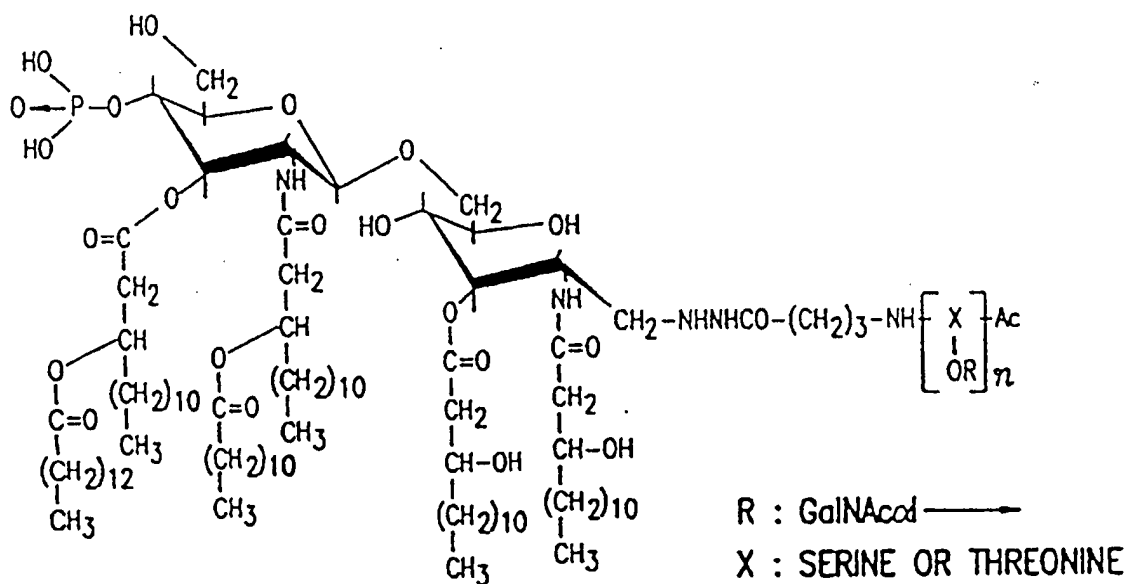


Reagents: i) NHS, EDC, CH₂Cl₂; ii) NH₂NH₂, MeOH; iii) DMF-H₂O.

FIG. 6A



MPL



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Reagents: i) NaCNBH_3 , NaHCO_3 , H_2O .

FIG.

6B

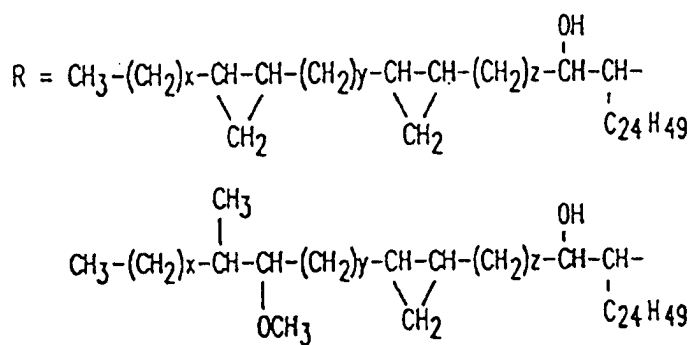


FIG. 7A

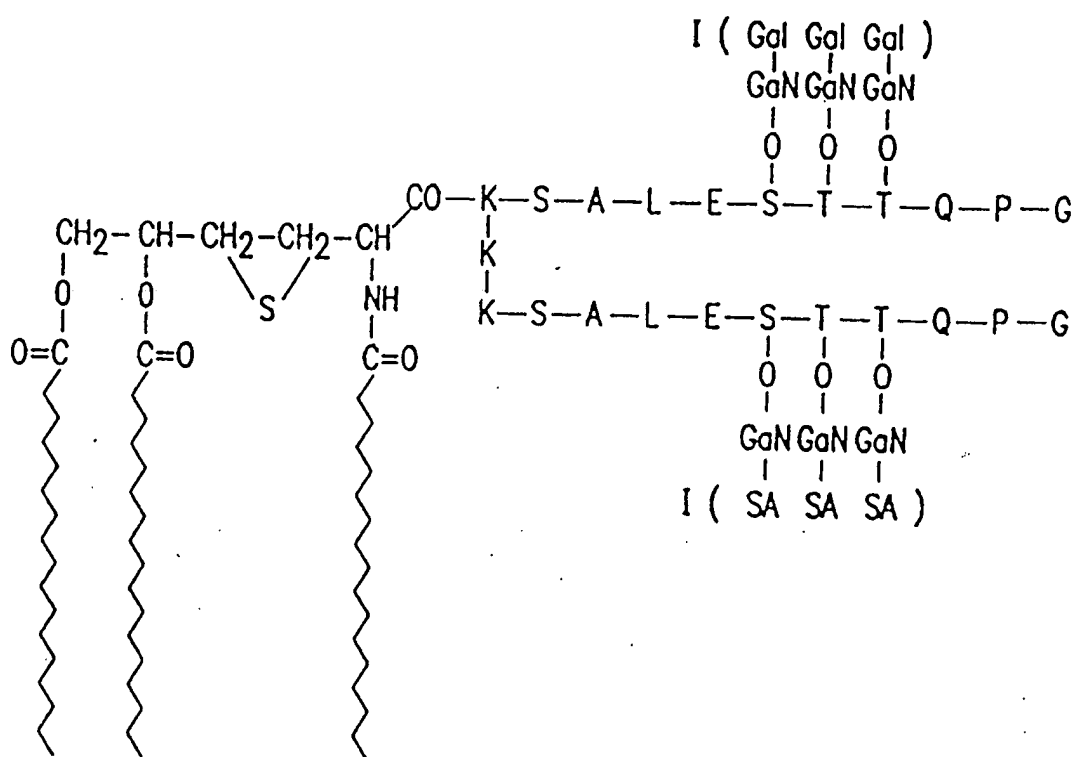
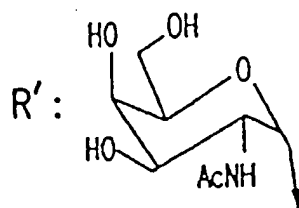
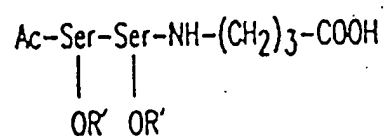
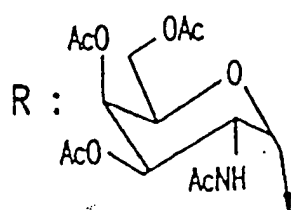
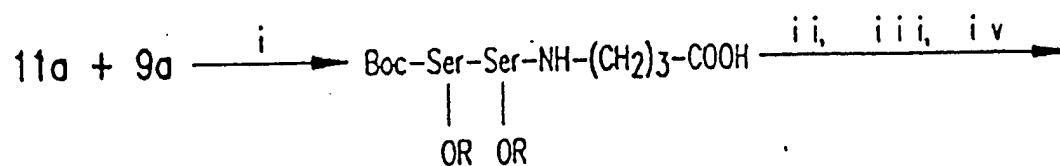


FIG.

7B



Reagents: i) Et₃N, DMF; ii) HCOOH; iii) Ac₂O, MeOH; iv) 10% 1N NaOH-MeOH, 5 min.

FIG. 8

Fig.9A

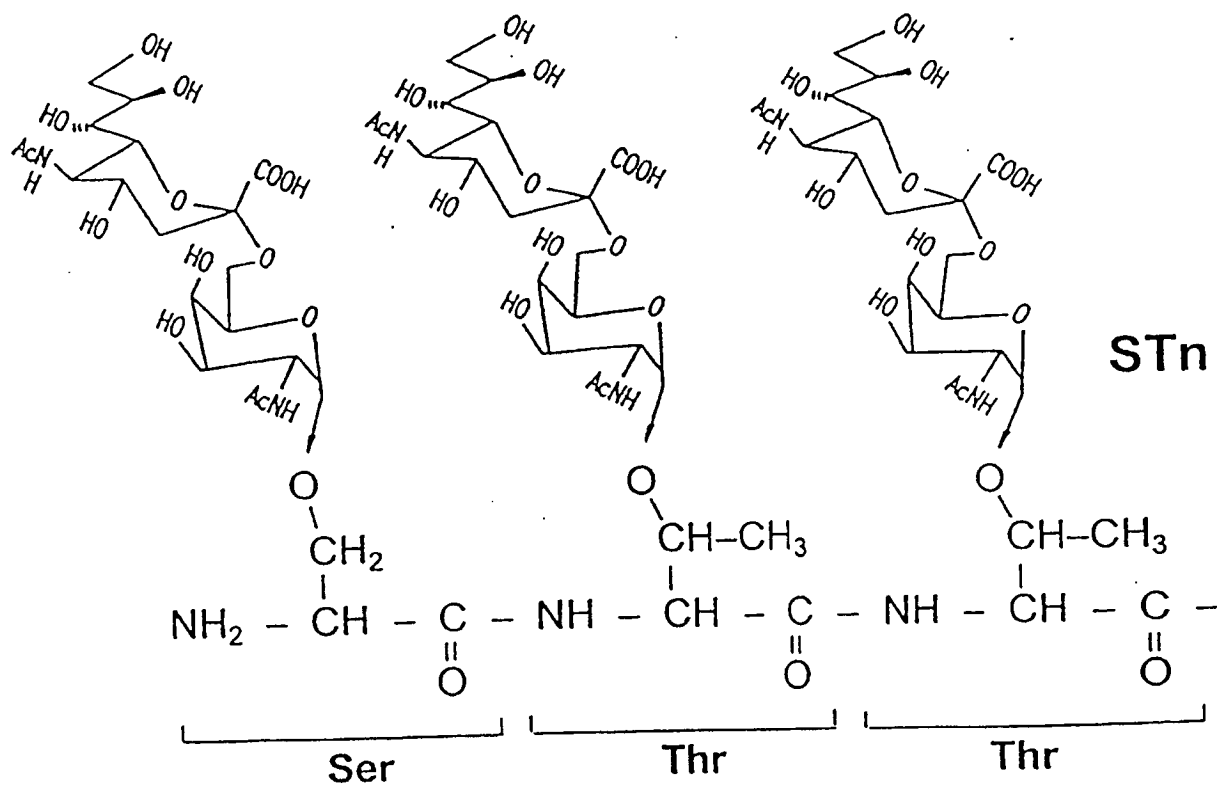
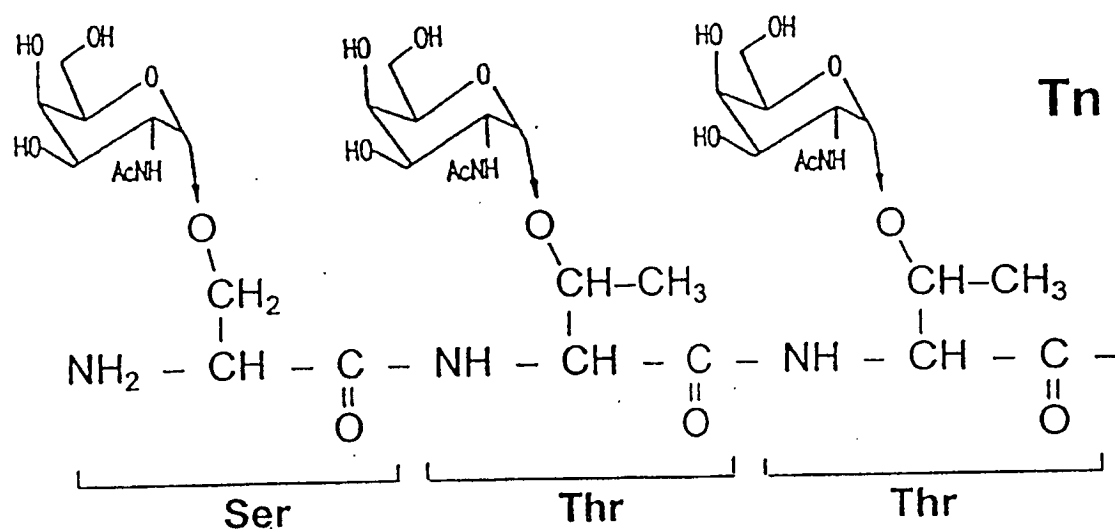
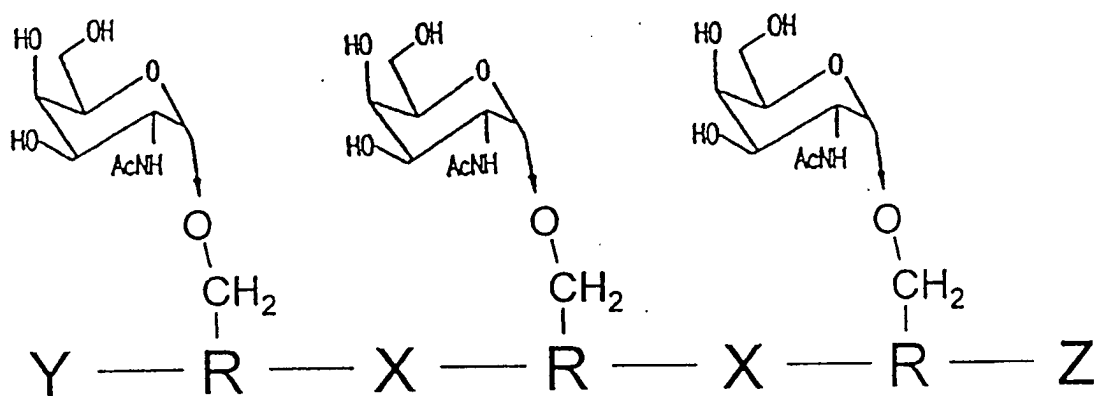


Fig. 9B



Y = terminal protected residue. X = spacer.

Z = active functional group ready to link to core or carrier molecule (e.g. activated carboxyl)

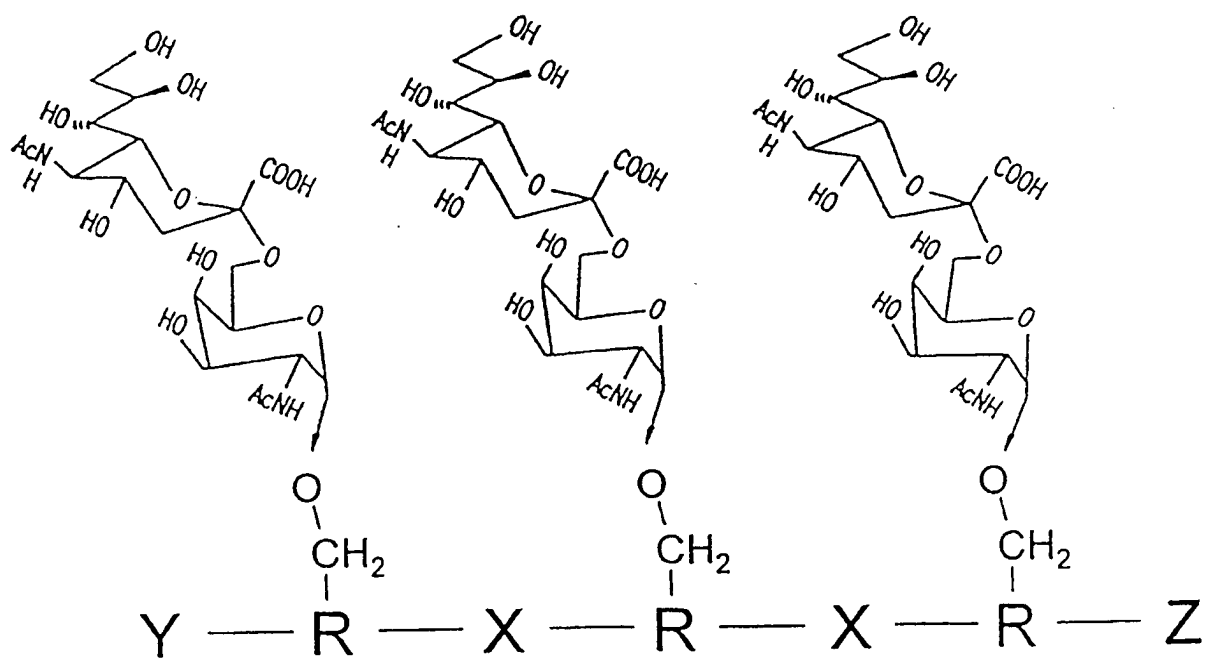


Figure 10

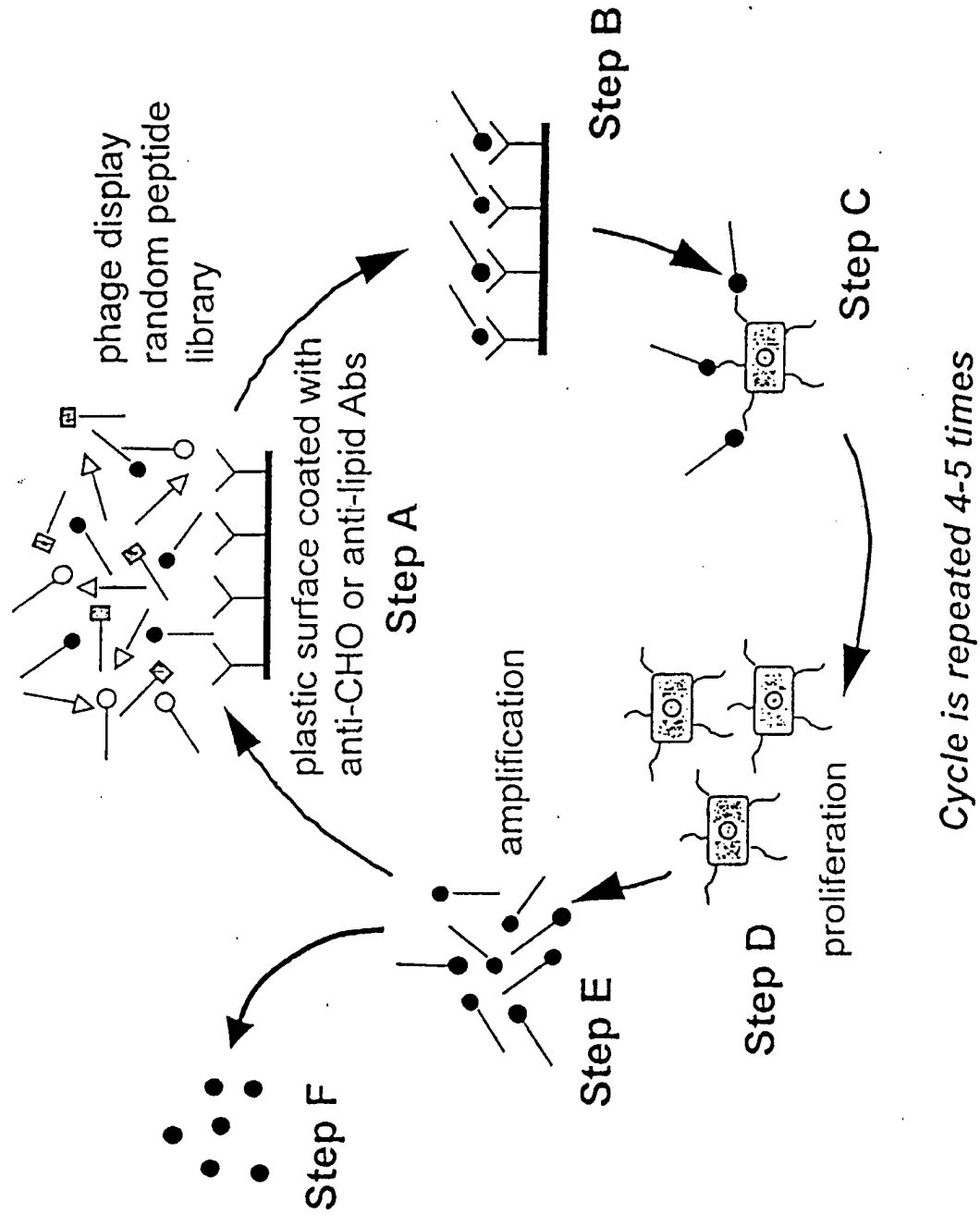


Figure 11A. Class II MHC restricted presentation of extracellular antigen to CD4+ T helper cells.

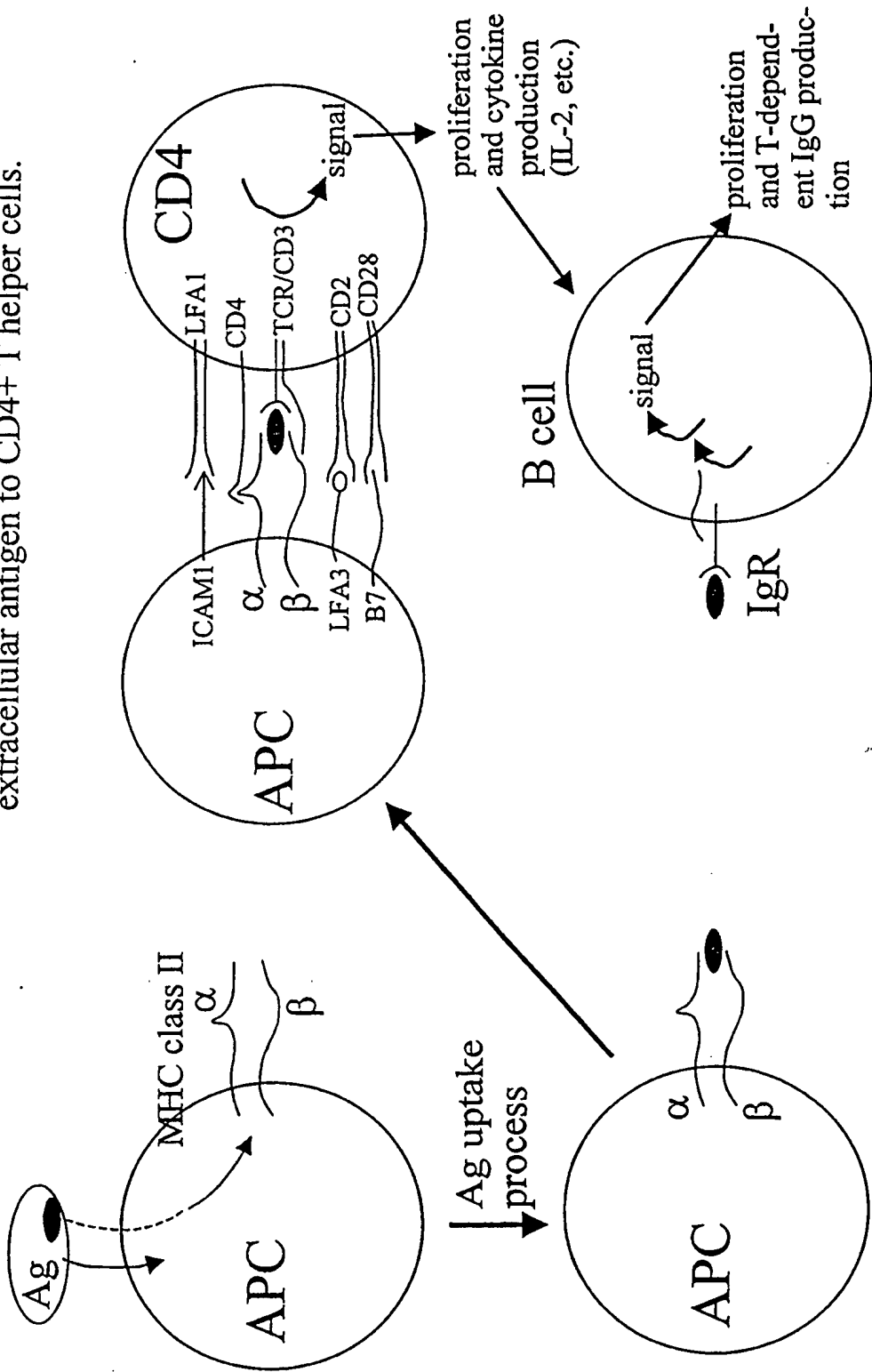


Fig. 12

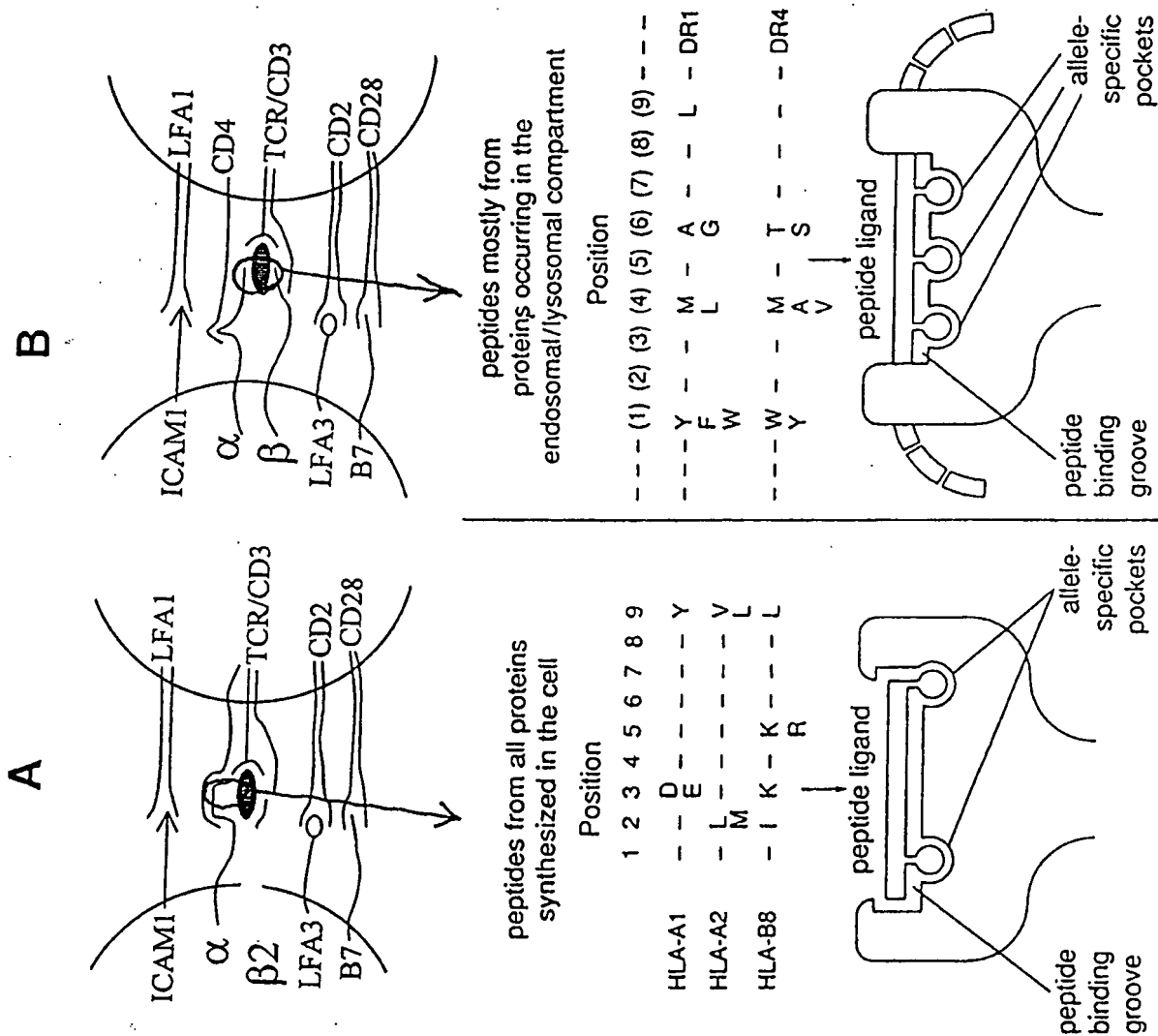


Figure 13

